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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/520,248	03/07/00	ABGRIGNANI S	CHIR-0234

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EXAMINER	
TUNG, M	
ART UNIT	**PAPER NUMBER**
1644	4

DATE MAILED: 10/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/520,248	Abgrignani
Examiner	**Group Art Unit**
Mary B. Tung	1644

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-11 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-11 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) 09/776,259 .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following minor informalities: On page 13 of the specification, the headings for each column appear to be out of alignment. It is presumed that the first column refers to IgM production, the second to IgG and the last to IgA. Clarification is required.

2. The use of the trademarks such as "FICOLL-HYPAQUE," page 7, line 35, "DYNABEADS," page 8, line 8, and so on, of the specification has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

3. Each letter of the trademarks must be capitalized. *See MPEP 608.01(V)* and *Appendix 1*.

4. The address of the American Type Culture Collection has changed. Applicants are required to amend the specification on page 8, line 2 to: ATCC , 10801 University Boulevard, Manassas, VA, 20110-2209.

Abstract

5. This application does not contain an Abstract of the Disclosure as required by *37 C.F.R. § 1.72(b)*. An Abstract on a separate sheet is required.

Claim Objections

6. Claims 8-11 are objected to because of the following informalities: text is missing from claims 8-11 because due to photocopying. Applicants are required to submit clean copies of the claims in response to this action.

7. Claims 3-11 are objected to under 37 C.F.R. 1.75(c) as being in improper form because multiple dependent claims are depending from other multiple dependent claims. See MPEP § 608.01(n). Applicants are required to amend the claims to eliminate the improper multiple dependencies recited in claims 3-8, 10 and 11.

Claim Rejections - 35 U.S.C. § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

9. Claims 1-11 are rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

10. It is unclear what the intended scope of claim 1 is. It is presumed that the claimed method is intended to encompass both in vivo and in vitro activation of T cells. It is unclear whether the method is intended to be limited to activation of purified populations of T cells, or if it encompasses activation of mixtures of cells (e.g. white blood cells) including T cells. It is also unclear whether antigen-independent activated T cells must eventually come into contact with processed antigen, or if the activated T cells are useful even if they do not specifically recognize antigens.

11. In claims 5 and 6 it is unclear to what the recited dosages refer. It is unclear whether for in vivo usage, a dosage of 100U/ml of IL-2 the concentration of IL-2 in the dose administered to a subject, or whether the concentration of IL-2 is in the blood or tissue fluid following administration and distribution into these compartments.

Claim Rejections - 35 U.S.C. § 102

12. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the Applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the Applicant for patent.

13. Claims 1-6 and 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Chong, (U.S. Patent 4,879,111).

Chong discloses a method of administration of IL-2 and TNF-alpha for treatment of infections. The instant claims do not exclude contact of T cells of a subject with an infection with the combination of IL-2 and TNF-alpha. Although the dosages

Applicant intends to use in vivo are unclear for the reasons discussed above in the rejection under 112/2 the dosages given in column 5 of the Chong appear to be comparable to the dosages recited in claims 5 and 6. The instant claims do recite "antigen independent activation of T cells" but this term does not distinguish over the prior art methods as any effects of IL-2 or TNF-alpha on T cells would be inherent to the prior art methods because they teach exactly the same method step: contacting T cells with IL-2 and TNF-alpha.

14. Claims 1-6 and 9-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Zimmerman et al. (U.S. Patent 5,425,940).

Zimmerman et al. disclose administration of a combination of IL-2 and TNF-alpha for treatment of tumors, see abstract. The dosages describe in col. 6 of the cited patent appear to fall within the same ranges as the dosages of IL-2 and TNF-alpha recited in instant claims 5 and 6.

Note: Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the Applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

Claim Rejections - 35 U.S.C. § 103

15. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-6 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chong, (U.S. patent 4,879,111) in view of Paul, Fundamental Immunology (1993).

Chong discloses a method of administration of IL-2 and TNF-alpha for treatment of infections. The instant claims do not exclude contact of T cells of a subject with an infection with the combination of IL-2 and TNF-alpha. Although the dosages Applicant intends to use in vivo are unclear for the reasons discussed above in the rejection under 112/2 the dosages given in column 5 of the Chong appear to be comparable to the dosages recited in claims 5 and 6. The instant claims do recite

"antigen independent activation of T cells" but this term does not distinguish over the prior art methods as any effects of IL-2 or TNF-alpha on T cells would be intrinsic to the prior art methods because they teach exactly the same method step: contacting T cells with IL-2 and TNF-alpha.

Assuming arguendo that the instant methods differ from those taught by the prior art on the basis of the language "antigen independent activation", then the cited secondary reference teaches that IL-2 and TNF-alpha both have effects on T cells independent of the presence of activation.

Paul teaches (page 766, col. 2) that IL-2 was originally termed "T cell growth factor" because it is capable of maintaining bone-marrow derived human T lymphocytes in exponential growth. Additionally, page 767, col. 2 of Paul teaches that IL-2 induces antigen-nonspecific lymphokine activated killer cells which appears to refer to activation of killer T cells via non-antigen-specific mechanisms. Therefore, depending on the Applicant's definition of the term "antigen independent activation" this term may apply to the effects IL-2 has on T cell growth. Paul additionally teaches that TNF-alpha (page 808, Table 2) induces IL-2 receptor expression in T cells and activates a variety of other cells involved in antigen-presentation.

One of ordinary skill in the art at the time the invention was made would have been motivated to contact populations of T cells with IL-2 or TNF-alpha, as taught by the '111 patent, in order to activate T cells independently of antigen by promoting antigen-independent growth of T cells via IL-2 and by upregulating IL-2 receptors on T cells thus augmenting the growth effects of IL-2 on non-antigen stimulated T cells, as taught by Paul. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. Further, as the claims are not limited to use of isolated T cell populations use of IL-2 and TNF-alpha would also be expected to activate other cells involved in T cell activation that are present in mixed T cell populations, such as macrophage, and thus indirectly up-regulate T cell activation for the purpose of providing activated T cells for therapeutic purposes.

17. Claims 1-6 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman, et al., (U.S. patent 5,425,940) in view of Paul, Fundamental Immunology (1993).

The '940 patent discloses administration of a combination of IL-2 and TNF-alpha for treatment of tumors, see abstract. The dosages describe in col. 6 of the cited patent appear to fall within the same ranges as the dosages of IL-2 and TNF-alpha recited in instant claims 5 and 6. The instant claims do recite "antigen independent activation of T cells" but this term does not distinguish over the prior art methods as any effects of IL-2 or TNF-alpha on T cells would be intrinsic to the prior art methods because they teach exactly the same method step: contacting T cells with IL-2 and TNF-alpha.

Assuming arguendo that the instant methods differ from those taught by the prior art on the basis of the language "antigen independent activation", then the cited secondary reference teaches that IL-2 and TNF-alpha both have effects on T cells independent of the presence of activation.

Paul teaches (page 766, col. 2) that IL-2 was originally termed "T cell growth factor" because it is capable of maintaining bone-marrow derived human T lymphocytes in exponential growth. Additionally, page 767, col. 2 of Paul teaches that IL-2 induces antigen-nonspecific lymphokine activated killer cells which appears to refer to activation of killer T cells via non-antigen-specific mechanisms. Therefore, depending on the Applicant's definition of the term "antigen independent activation" this term may apply to the effects IL-2 has on T cell growth. Paul additionally teaches that TNF-alpha (page 808, Table 2) induces IL-2 receptor expression in T cells and activates a variety of other cells involved in antigen-presentation.

One of ordinary skill in the art at the time the invention was made would have been motivated to contact populations of T cells with IL-2 or TNF-alpha, as taught by the '940 patent, in order to activate T cells independently of antigen by promoting antigen-independent growth of T cells via IL-2 and by upregulating IL-2 receptors on T cells thus augmenting the growth effects of IL-2 on non-antigen stimulated T cells, as taught by Paul. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. Further, as the claims are not limited to use of isolated T cell populations use of IL-2 and TNF-alpha would also be expected to activate other cells involved in T cell activation that are present in mixed T cell populations, such as macrophage, and thus indirectly up-regulate T cell activation for the purpose of providing activated T cells for therapeutic purposes.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

19. A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.130(b).

20. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

21. Claims 1-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,074,635.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the instant claims encompass the *in vitro* methods claimed in the '635 patent. Additionally, the '635 patent teaches the same dosages and the claims are directed to methods of using the combination of IL-2 and TNF-alpha to activate T cells independently of antigen.

Allowable Subject Matter

22. No claim is allowed.

Conclusion

23. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

24. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344. The Examiner can normally be reached Tuesday through Friday from 8:30 am to 6:00

pm and on alternating Mondays. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

September 29, 2000
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640